

### REMARKS

Claims 1 and 3 to 11 are currently pending and under examination in the application. By the present amendment, claims 1 and 3 are amended to recite that the nucleic acid is single-stranded. Support for this amendment is provided throughout the specification as filed and does not constitute new matter. This amendment is made without acquiescence to the rejection and without prejudice to pursuing the encompassed subject matter in a related divisional, continuation, or continuation-in-part application.

### Interview Summary

Applicants kindly thank Examiners Tung and Horlick for sharing their time with Applicants' representatives in a telephonic interview on December 1, 2009. During this interview, Applicants' representatives discussed the inventive features of the presently claimed subject matter, particularly in view of the lack of expectation in the art at the time of filing with regard to successfully performing bisulfite reactions on nucleic acid bound to a solid phase, as evidenced by the previously submitted Declaration of Dr. Markert-Hahn. A copy of slides submitted to the Examiners in advance of the telephonic interview is attached.

### Rejections under 35 U.S.C. § 103

A. The Examiner rejected claims 1 and 3 to 5 under 35 U.S.C § 102(a) for alleged obviousness over Herman *et al.* (U.S. Patent No. 5,786,146, issued July 28, 1998) in view of Gerdes *et al.* (U.S. Patent 6,291,166, issued Sep. 18, 2001). The Examiner agreed at page 2 of the Action that Herman *et al.* do not disclose that a nucleic acid is bound to a solid phase and then the nucleic acid is deaminated. The Examiner asserted, however, that Gerdes *et al.* disclose a method of using solid phases to irreversibly capture RNA or DNA and teaches true, direct solid phase manipulation and analyses including enzyme recognition, hybridization and amplification. The Examiner then asserted that one of ordinary skill in the art would have been motivated to apply a solid phase bound DNA as taught by Gerdes *et al.* in the method of Herman *et al.* because, as taught by Gerdes *et al.*, a solid phase bound nucleic acid can be directly and

conveniently manipulated and can be applied in various ways. The Examiner further asserted that such a combination would have been *prima facie* obvious at the time of filing.

Applicants respectfully traverse this rejection and submit that the instant claims satisfy the requirements of non-obviousness. In particular, Applicants submit that the Examiner has not established a *prima facie* case of obviousness with respect to the presently claimed subject matter. See *In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997) ([T]he USPTO has the burden of showing a *prima facie* case of obviousness). The Examiner must at a minimum demonstrate that the cited references teach or suggest all the claim features, and even assuming, *arguendo*, that the references teach each claim feature, the Examiner must provide an explicit, apparent reason to practice these features in the fashion claimed by the Applicants with a reasonable expectation of success. See *KSR v. Teleflex, Inc.*, No. 04-1350 at 4, 14 (U.S. Apr. 30, 2007) (“A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art”). Here, the Examiner has not shown that the cited references even contemplate performing a deamination reaction on a nucleic acid bound to a solid phase, let alone has the Examiner established the requisite motivation to practice the presently claimed subject matter with a reasonable expectation of success.

As acknowledged by the Examiner at page 2 of the Action, Herman *et al.* fail to teach or even remotely suggest the active, recited step of performing a deamination reaction on a nucleic acid bound to a solid phase. To the contrary, Herman *et al.*, at best, perform deamination reactions in solution. Gerdes *et al.* do not remedy the defects in Herman *et al.* Gerdes *et al.* is entirely silent on the use of the solid phase techniques described therein for use in bisulfite modification reactions. Gerdes *et al.*, at best, mention the use of solid phase matrices in purification methods to irreversibly capture RNA or DNA, and solid phase manipulation and analyses including enzyme recognition, hybridization and amplification. Gerdes *et al.* relates to a method of irreversibly binding and thus, permanently archiving, nucleic acid from specimens, thus allowing re-analysis of the same nucleic acid specimen an unlimited number of times, which is especially useful when the specimen is available in limited quantity or cannot be replaced (see, e.g., column 2, lines 43-45 and column 4, lines 22-26 of Gerdes *et al.*). However, as noted previously, the utility of the invention described in Gerdes *et al.* requires that the nucleic acid is

neither altered nor exhausted during analysis (see, e.g., column 2, lines 45-47 of Gerdes *et al.*). This utility, however, in no way relates to chemically modifying nucleic acid molecules as recited in the instant claims. Indeed, what is suggested in Gerdes *et al.* as “direct solid phase manipulation” (see, e.g., column 3, lines 39-49 of Gerdes *et al.*) is in fact limited to a manipulation of the solid phase bound nucleic acid by enzyme, hybridization, and/or amplification reactions (see, e.g., column 4, lines 45-48 of Gerdes *et al.*). None of the exemplary uses described in Gerdes *et al.* relate to modifying nucleic acid molecules as presently claimed, *i.e.*, carrying out a bisulfite reaction on solid-phase bound nucleic acid whereby the nucleic acid is deaminated. Gerdes *et al.*, therefore, fail to teach or suggest the use of solid phase immobilization, as described therein, with a nucleic acid modification reaction, such as with the bisulfite reaction recited in the instant claims. Accordingly, the cited references fail to teach deamination of a single-stranded nucleic acid bound to a solid support.

Furthermore, even assuming *arguendo* that each feature recited in the instant claims was known in the art, the Examiner has still failed to establish a *prima facie* case of obviousness, since the Examiner does not provide a sufficient reason as to why the skilled artisan would combine the teachings of the prior art to practice the claimed invention with any reasonable expectation of success. In fact, at the time of filing, the skilled artisan would have had no expectation of successfully performing a bisulfite reaction on single-stranded nucleic acids bound to a solid support. Instead, they would have believed that such a reaction would produce no useful results whatsoever. Indeed, at the time of filing, bisulfite ions were believed to interact only with cytosines that do not participate in base-pairing. However, single-stranded DNA was believed to interact with a solid phase as if it were participating in base-pairing. Thus, bisulfite ions were not expected to be able to physically interact with the cytosines in single-stranded DNA bound to a solid phase. Since bisulfite ions must physically interact with the cytosines in DNA to achieve deamination, a person skilled in the art at the time of filing would have expected a bisulfite reaction performed on a single-stranded nucleic acid bound to a solid phase to produce no useful results, whatsoever. This understanding on the part of the skilled artisan is clearly set forth in the previously submitted Declaration of Dr. Markert-Hahn (see, e.g., Items 5 and 12 of the Declaration with the Amendment/Response filed April 15, 2008).

As further evidence of the understanding of the skilled artisan at the time of filing the instant application, Applicant submits with this amendment the Declaration of Matthias Ballhause, which confirms the statements made by Dr. Markert-Hahn in the Declaration filed April 15, 2008, namely that at the time the instant application was filed, one of skill in the art would not have reasonably expected that a denatured nucleic acid bound to a solid phase could have been subjected to bisulfite treatment, for reasons described in detail at Item 6 of the Declaration of Matthias Ballhause. Mr. Ballhause also provides published scientific articles that reflect this understanding. These include Hayatsu *et al.* (copy attached), which describes that bisulfite is a single-strand specific, cytosine deaminating agent, and that the single-strand specific nature of this chemical reaction was retained for DNA complexed with chitosan (page 1365, right column, second full paragraph). Likewise, Olck *et al.* describes that the bisulfite treatment was performed under conditions maintaining that DNA in the single stranded form so as to ensure optimal bisulfite reactivity (Abstract). Clearly, these references point to the single-stranded nature of the nucleic acid as being important or critical to the bisulfite reaction, so it immediately follows that persons of skill in the art, having the understanding that single-stranded nucleic acids bound to a solid support lose their single-strand nature, would believe that single-stranded nucleic acids bound to a solid support would not be amenable to bisulfite reaction. Indeed, according to Mr. Ballhause, it was a surprising and unexpected finding that single-stranded DNA bound to a solid phase could be accessed by bisulfite ions (Item 8).

In view of the understanding in the art at the time of filing, as evidenced by both the Declaration of Dr. Markert-Hahn, the Declaration of Matthias Ballhause, and scientific publications, as discussed above, it is clear that a person skilled in the art at that time would have had no expectation of successfully performing a bisulfite reaction on a single-stranded nucleic acid bound to a solid support with any, let alone the requisite reasonable expectation of success. Applicants further submit that the Declarations must be considered to have substantial probative value, particularly considering the factual support provided by the cited scientific publications. Accordingly, the cited references, alone or in combination, fail to render obvious the instant claims.

Applicants further submit that the claimed methods offer surprising and unexpected advantages over the prior art, and that these advantages are secondary factors that further establish the non-obviousness of the claimed invention. As described in the Declaration of Matthias Ballhause, it was both surprising and unexpected that the single-stranded DNA bound to a solid phase could be accessed by bisulfite ions (Item 8).

Since the requisite elements of a *prima facie* case of obviousness are missing, Herman *et al.* and Gerdes *et al.*, alone or in combination, fail to establish a *prima facie* case of obviousness over the presently claimed subject matter. Therefore, the instant claims satisfy the requirements of non-obviousness, and Applicant respectfully requests withdrawal of this rejection under 35 U.S.C. § 103(a).

B. The Examiner has maintained the rejection of claims 6 to 11 under 35 U.S.C. § 103(a) for alleged obviousness over Herman *et al.* in view of Gerdes *et al.* (as applied to claims 1 and 3 to 5 in section A above), and further in view of Weindel *et al.* (WO 01/37291, issued May 21, 2001). The Examiner agreed that Herman *et al.* do not disclose that the solid phase comprises a magnetic glass particle, a magnetic glass particle having a diameter between 0.5µm and 5µm, or the magnetic glass particle manufactured by the sol-gel method. However, the Examiner asserted that Weindel *et al.* disclose a magnetic glass particle, which can be used in nucleic acid purification. Further, the Examiner asserted that Weindel *et al.* disclose that the magnetic glass particle is a solid dispersion of small magnetic core in glass, the diameter of the particle is between 5 and 500nm, and the magnetic glass particle is used in nucleic acid purification from a sample containing cells. Still further, the Examiner asserted that Weindel *et al.* disclose that the advantage of this is its potential simplicity and high sensitivity. The Examiner then asserted that one of ordinary skill in the art would have been motivated to apply the magnetic glass particle of Weindel *et al.* in the method of Herman *et al.* as a solid support for converting cytosine bases to uracil bases in a nucleic acid because of the advantage of using the magnetic glass particle. The Examiner further asserted that such a combination would have been *prima facie* obvious at the time of filing.

Applicants traverse this rejection and submit that the instant claims satisfy the requirement of non-obviousness over the cited references. In particular, Applicants submit that Herman *et al.*, Gerdes *et al.*, nor Weindel *et al.*, alone or in combination do not teach or describe performing a deamination reaction on a nucleic acid bound to a solid phase, and the Examiner has not established the requisite motivation to practice the presently claimed subject matter with a reasonable expectation of success.

For the reasons discussed in section A above, Applicants submit that Herman *et al.* and Gerdes *et al.* fail to teach or in any way suggest the active recited step of incubating the solid phase bound nucleic acid in the presence of sulfite ions whereby the nucleic acid is deaminated, as recited in independent claim 1, from which the instant claims depend. Weindel *et al.* also does not remedy this deficiency, as this reference is silent with respect to performing deamination reactions on solid phase bound nucleic acid, let alone on magnetic glass particle bound nucleic acids, as recited in claims 6 to 11. In fact, Weindel *et al.* is limited to teaching the use of the magnetic glass particles described therein for either nucleic acid purification protocols or standardized nucleic acid amplification reactions. Thus, in failing to teach or suggest each feature of the instant claims, the cited references in combination fail to establish the minimum requirements of a *prima facie* case of obviousness.

Moreover, even if a person skilled in the art at the time of filing combined the methods of Herman *et al.*, Gerdes *et al.*, and Weindel *et al.*, the person would not arrive at the presently claimed subject matter with any reasonable expectation of success. The combination proposed by the Examiner simply does not teach a person skilled in the art to perform deamination reactions on solid phase, as recited in independent claim 1, but instead teaches that person to perform such reactions in solution, if effect teaching away from the presently claimed methods. Thus, a person skilled in the art at the time of filing would have had to embark on a whole new line of experimentation to arrive at the presently claimed method, which would have required that person to go against the expectations in the art at the time of filing, as discussed in section A above.

Given the deficiencies in Herman *et al.*, Gerdes *et al.*, and Weindel *et al.*, these references, alone or in combination, fail to render the instant claims obvious. Consequently, the

instant claims satisfy the requirements of non-obviousness, and withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,  
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Enclosures:

Declaration of Matthias Ballhause  
Hayatsu *et al.*  
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